REMARKS

With this response, Claims 1-18 and 24-41 are pending, of which claims 16-18, 21-23, and 38-40 are withdrawn from consideration as being drawn to non-elected species. However, Applicants reserve the right to have the withdrawn claims examined upon indication of an allowable generic claim.

I. Withdrawal of Rejections

Applicants thank the Examiner for indication of the withdrawal of the prior art rejections of the claims set forth in the previous Office Action.

II. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-15, 24-37 and 41 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way so as to enable those skilled in the art to make and/or use the invention. This rejection is respectfully traversed for at least the reasons which follow.

In support of the rejection, the Examiner asserts that "the specification does not teach to measure postprandial triglyceride levels, and to use such as an indicator for any diagnostic purpose, nor any working example suggesting the same." Applicants respectfully disagree.

While the background of the invention discusses the measurement of fasting triglyceride levels, it also discusses the observed association of elevated postprandial triglyceride levels with cardiovascular disease and the effects of exendins on the postprandial triglyceride levels of diabetics. *See Specification*, page 4, third full paragraph, including the references cited therein, and Example 186. The specification also discusses the association of elevated triglyceride levels with various disease states, including diabetes, pancreatitis, and cardiovascular disease. *See Specification*, pages 2-4. Moreover, the invention is described as including the modulation of fasting triglycerides, the modulation of postprandial triglyceride levels, as well as the modulation of both fasting and postprandial triglyceride levels. *See Specification*, paragraph bridging pages 12 and 13. Further, elevated triglyceride levels are discussed as "any degree of

triglyceride levels that is determined to be undesirable or is targeted for modulation." *Specification*, page 12, first full paragraph.

Taken in combination, such disclosure provides adequate direction to those skilled in the art of how to make and use the claimed invention. For example, the specification discloses the association of elevated postprandial triglyceride levels with various disease states and disorders, as well as the lowering of postprandial triglycerides levels by way of description and example, including ascertaining an initial state of postprandial triglyceride levels. It is submitted that such disclosure necessarily includes the step of identifying target subjects with elevated postprandial triglyceride levels, *i.e.*, postprandial triglyceride levels that are determined to be undesirable or targeted for modulation.

In this regard, *elevated* postprandial triglyceride levels are those postprandial triglyceride levels which are *elevated* compared to the normal range of postprandial triglyceride levels. Such elevated postprandial triglyceride levels are discussed in the references cited in the background of the invention related to the discussion of elevated postprandial triglyceride levels mentioned above (cited in the Information Disclosure Statement filed April 11, 2001). Thus, contrary to the Examiner's allegation that "the method of the invention does not distinguish healthy subjects who are having transiently elevated triglyceride levels associated with food intake, . . . from those who have pathologically elevated triglyceride levels associated with a disease or a disorder," the specification does teach the identification of subjects with *elevated* postprandial triglyceride levels, vis-à-vis normal postprandial triglyceride levels.

More specifically, the cited references discuss an association between impaired metabolism of postprandial triglyceride-rich lipoproteins and the presence or development of coronary artery disease. *See, e.g.*, Karpe, *J. Int. Med.* (1999) 246:341-355. There is extensive discussion of studies investigating the effects of elevated postprandial triglyceride levels on health, including various methodologies for assessing postprandial triglyceride levels. It is well established that in the context of enablement that a patent application "need not teach, and preferably omits, what is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir.

1986) citation omitted. Further, Example 186 of the present application illustrates the effects of exendin on postprandial circulating triglyceride levels in diabetic subjects, *i.e.*, subjects suffering from a disease state associated with elevated postprandial triglyceride levels, including area under the curve values as well as peak postprandial triglyceride concentrations. Taken in combination with the knowledge of those skilled in the art, the specification provides adequate guidance regarding the identification of subjects with elevated postprandial triglyceride levels as an indicator of selection for the therapeutic lowering of triglyceride levels.

As such, it is submitted that Applicants have provided considerable direction and guidance, and have presented working examples such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation. The Examiner has not provided sufficient evidence to cast doubt on the guidance provided in the specification. Rather, the Examiner has provided generalizations regarding a lack of predictability in the art and the need for some experimentation to "identify a subject in need of lowering the elevated triglyceride levels among those having elevated postprandial triglyceride levels.

Even assuming, *arguendo*, that the Examiner's generalization regarding the unpredictable state of the art is accepted, the conclusion that undue experimentation would be required is inconsistent with the current state of the law. Specifically, the law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174, (Int'l Trade Comm'n 1983) *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In this regard, based on the teachings of the present specification and the knowledge of those skilled in the art, a trained clinician is more than capable of identifying a subject with elevated postprandial triglyceride levels in need of lowering.

An analysis of the *In re Wands* criteria also supports Applicants' position that no undue experimentation would be required to make and use the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1998). The first *Wands* criterion is the quantity of experimentation necessary. The "make-and-test" quantum of

experimentation is reduced by the extensive knowledge to which a person of ordinary skill in the art has access. Performing routine and well-known steps, such as clinical assays to determine plasma triglyceride levels in a postprandial state, cannot create undue experimentation, even if it is laborious. *See In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-219 (CCPA 1976).

The second and third *Wands* criteria relate to the amount of direction or guidance given, and the presence or absence of working examples. As discussed above, the present specification provides ample guidance and direction in the form of, *e.g.*, the a discussion of the association between elevated postprandial triglyceride levels and various disease states and disorders, the modulation of postprandial triglyceride levels, and working examples showing the same.

The fourth, fifth, and sixth *Wands* criteria focus on the nature of the invention, the state of the art, and the relative skill in the art. The present invention relates to methods for lowering postprandial triglyceride levels in a subject with elevated postprandial triglyceride levels by administering exendin compounds. Considerable knowledge and resources guide practitioners in this art as to the conditions and approaches that can be utilized to perform such therapeutic methods, as evidenced by the references cited in the specification and the additional references made of record.. Many resources are readily available to the skilled art worker. Moreover, as discussed above, the present specification itself adds to the relative skill in the art by providing detailed guidance regarding the application of such techniques to the art of the present invention. Such resources, combined with the specification and the general knowledge of those skilled in the art provide ample guidance to enable one of ordinary skill in the art to make and use the claimed invention.

The seventh criterion considers the predictability of the art. The Examiner alleges that "the state of the prior art has established that triglyceride levels vary in response to meals, hence postprandial triglyceride levels would not be suitable as an indicator for identifying a subject in need of lowering triglyceride levels, i.e., lack of predictability." The Examiner appears to rely on the concept that because postprandial triglyceride levels are transient, measurement of such levels can never serve as an indicator of therapeutic

treatment. However, as discussed in the present specification and in the cited art, certain disease states and disorders are known to be associated with elevated postprandial triglyceride levels. Recognition of such an association necessarily includes an assessment of what amounts to elevated postprandial triglyceride levels.

Even assuming, *arguendo*, that the Examiner's allegation is accurate, determination of procedures and protocols to assess elevated postprandial triglyceride levels is well within the level of skill in the art. Further, it is submitted that the specification discloses sufficient guidance to render the results predictable within the context of the invention. In fact, by providing guidance as to the association of certain disease states and disorders with elevated triglyceride levels, the discussion of the modulation of postprandial triglyceride levels, and exemplification of the same, Applicants have demonstrated that the present invention yields a predicted result.

The eighth criterion focuses on the breadth of the claims. Enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck,* 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In the present case, one of skill in the art is specifically guided by the disclosure of a method of lowering postprandial triglyceride levels in a subject in need thereof, including identifying such a subject, *i.e.*, those with elevated postprandial triglyceride levels. As such, based on the teachings of the specification, one of skill in the art would be able to ascertain which subjects exhibit elevated postprandial triglyceride levels as a target for therapeutic lowering, thereby possessing the disclosed utility and falling within the scope of the claims. It is thus submitted that the specification provides enablement commensurate in scope with the claims.

Accordingly, for at least these reasons, it is submitted that the claims are sufficiently enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-5068 should any additional information be necessary for allowance.

Respectfully submitted,

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